randomization possibly being problematic. I mean, every study that I'm involved in, I can actually produce a randomization table to show you how the study -- how the subjects were going to be allocated.

Doesn't the sponsor have the original randomization table that would show that this unfortunate streak is part of --

MR. KOTZ: Right. In this study, unfortunately, was randomized. They did not use block randomization. And the randomization was done with envelopes. They were just -- the Company was given a stack of envelopes, and they were just identified -- the envelopes were just identified as to age and to treatment.

I mean, the numbers were calculatedby age and treatment, but they were just given a 30 --

DR. D'AGOSTINO: But when I -- like I said, when I mastered the randomization, I do stuff things in the envelopes. But I also have a list of what went in the envelopes.

MR. KOTZ: I don't know. That I have no idea. I would have to check with the Bio and Research Monitoring Group who checks these -- premonitors these studies. And I want -- as far as the randomization goes, I want to, you know, clarify the record --

correct the record.

It was on the Alabama site, which had 11 patients in a row which were randomized to CryoGen -- wait, I'm doing it again. It was Alabama, which had 13 out of the 14 patients randomized to CryoGen, and the Denver site, which had 11 patients in a row randomized to CryoGen.

DR. BLANCO: Are you sure you don't want to wait until after lunch to make sure that's correct? Let me clarify -- 1 want to go back to what Dr. D'Agostino brought up, because I'd like to hear an answer for this afternoon.

And I think what he's saying -- and I don't believe I heard a good answer from you. I'm sorry, and maybe the Company needs to address this. But I think what he's saying is -- I mean, yes, you've got envelopes. What did you do, shuffle the envelopes'?

No, you usually stuff the envelopes based on some sort of list that a computer prints out that gives you a set of random numbers. I think what he's saying is, you know, if we're questioning whether the randomization was altered, which might alter the results of the study, then one way to answer that would be to say, "Hey, here was our randomization.

And it came up with that particular bad break of 11 patients in a row being put in one group."

So I think I still would like to see that addressed this afternoon. Okay? When we come back. so either by the FDA or by the Company, whether there is some documentation that we had a roll of 11 that all went in to one group. Is that fair enough, Ralph?

DR. KATZ: This is just a quick interpretive question follow up to -- if we're going to revisit power. How success is defined by a self-evaluation PBAC score of 75, and how do we take into account the natural variability and self-interpretation as a criterion for success?

Perhaps that can come up in the wash when we talk about power after lunch.

DR. BLANCO: Okay. Let's bring that up, but I'm not sure there's an answer right off the bat, other than it's a validated system. But we can bring that up. That's more discussion. Barbara -- Dr. Levy.

DR. LEVY: I have two questions. One is the temperature probe data that were done in hysterectomy. Were those patients pre-treated with Lupron? They were not. So my question is, is that a valid assumption for patients who are pre-treated, the

endometrium is thinned, and can we have confidence in those temperature data. So that's my first question.

The second one is of interest that one of the sites with the very lowest success rates was also the site, I think, that was done in office. And presumably, therefore, the site that was done with most of the local anesthetic, or local with sedation.

And so I have some concerns about making any statements about anesthesia requirements when it appears that the site using less anesthetic, using the local anesthetic and the local with sedation, may indeed have much lower success rates. And I'd like to hear some comment and discussion about that.

DR. BLANCO: All right. Let me -- we're really kind of getting into discussion, I think, more than issues of fact. So unless somebody else has a question specific for clarification of an issue of fact, which I don't see, let's bring that up during the discussion session and we'll try to address that.

It's 12:00 noqn. Let's have a 45-minute lunch. We will meet back and start promptly at 12:45. Thank you.

(Whereupon, the foregoing matter went off the record at 12:02 p.m. and went back on the record at 12:55 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:55 p.m.)

DR. BLANCO: All right. We're going to go ahead and start the afternoon session, and the first item of the afternoon session is the Panel deliberations.

But this is what we're going to do for the afternoon. We're going to ask the Company and FDA to go over the questions that were brought up in the morning and see what answers they were able to put together. Then we're going to go over all the questions that the FDA would like the Panel members to address. We'll just go through them, read them, so that we know all of the different items. And then we'll go back and discuss each question, item by item.

We will then open the forum again for the public to make comments, the Company to make some comments. Then we'll come back. We'll go over the voting options and the definitions of the different issues, and then we'll take a vote, and we'll call it an afternoon. And probably we'll have a break in there somewhere in between. Okay?

So let's go ahead and start with the issues that were brought up, questions from this morning. And this is just the order in which I wrote

them down, but the first question that was brought up was the issue of adverse effects and whether there was a preponderance of the adverse effects at the two sites that seemed to have a different rate of success than the other sites.

MR. LEWIS: Hello. My name is Steve Lewis. I'm a consulting statistician. I have no financial interest in the Company other than a fee for service agreement. Over the lunch break, we took a quick look at the adverse events, and what I can tell you is we see no indication that there is a preponderance of adverse events in the two sites that had the lowest adverse event rates.

DR. BLANCO: That had the lowest --

MR. LEWIS: I'm sorry, that had the lowest success rates. I'm sorry.

DR. BLANCO: Okay. Let's see, whose question was that?

MS. YOUNG: That was mine.

DR. BLANCO: Okay. Any other issues you want to follow up on that, Diony? No, okay. All right, thank you.

The second question that I had was Dr. D'Agostino's issue about the control arm had an 85 percent expected success rate the way the study was

designed. Does the fact that the control arm achieved a lower success rate in the actual clinical study alter the statistical analysis? Did I say that right, Ralph?

DR. D'AGOSTINO: Yes.

DR. BLANCO: Okay.

MR. LEWIS: Steve Lewis again. The powering of the study was based on efficacy of valuable patients, not on intention to treat. If you look at the success rate based on efficacy of valuable, I believe it's about 81 percent for the rollerball group, and we believe that's consistent with the modeling assumptions and what's known about the procedure.

DR. D'AGOSTINO: That's right. And I guess the question I was raising, and I think that's the appropriate answer for this particular setting, but I think in terms of the Panel and the whole notion of these non-inferiority trials or equivalency trials, that not only do you want to have some priority statement about the delta but also about the expected rates and the intent-to-treat population is usually or quite often the population that people are thinking about, at least statisticians, in terms of their computations. so I don't fault you for what you

presented. I think what you presented was fine. I'm just raising a bigger question in terms of how to interpret these type of studies.

MR. LEWIS: Thanks. We'll note that for future trials.

DR. BLANCO: All right. Thank you. Anything else, Ralph?

DR. D'AGOSTINO: No.

DR. BLANCO: Okay. The next question that I had from the morning was the issue of the temperature data where we're referring specifically to where the probes were on the outside of the uterus and temperature was not shown to vary, and the fact that those patients did not have Lupron pre-treatment versus the patients that were undergoing the actual clinical procedure did seem to have the Lupron pre-treatment.

DR. DULEBA: I will answer this question. My name is Antoni Duleba. I am from Yale University. I do not have any financial interest in the Company, but I have been reimbursed for participating in this meeting.

I think there are two answers or two reassurances that we can provide with regard to the thermal effect of the instrument in clinical trials.

First is that indeed in spite of a fairly large number of patients treated during the trial and subsequent number, around 300, commercial treated with this device, there was not a single report of injury suggestive of thermal damage to the serosa or surrounding organs.

The secondpiece of reassuring information is from the fact that we observed, actually, the front of the ice under the ultrasound, which is a unique feature of the freezing procedures in contrast to the heating procedures where we really are not sure how far the heat penetrates. So those are the two indirect but quite reassuring pieces of information I can offer.

DR. BLANCO: Barbara? Dr. Levy?

DR. LEVY: Yes. I think with respect to this particular device and this particular trial, I think you're probably correct. I think some of your data are showing us that via ultrasound monitoring will vary in clinical use. I think that that's clear just looking at your study sites. And we have to assume that your study sites are the best of the best and that when this thing gets out there on the market it will be probably used in less than ideal circumstances. So I'm a little less reassured by

that.

The fact that you've treated somewhere close to 200 patients without an adverse event is nice, but from a scientific standpoint, when we're trying to demonstrate clinical safety, clinical safety should be tested under the same circumstances in which the device is going to be used. And I think that's very, very important for us when we're looking at things. If it was tested under conditions that are different than the conditions under which they're going to be used, that raises a question.

DR. DULEBA: I can add one piece of information. It's extremely important, of course, to be as close to real life in testing, but in those particular patients who were treated prior to hysterectomy, it would have been very difficult to convince patients to undergo yet another therapeutic intervention, i.e. getting Lupron, months prior to the procedure.- so for those reasons, it was chosen not to do so. But, indeed, this is a limitation of the design of these kind of studies. Thank you.

DR. BLANCO: Again, let me address the issue, and I don't think that there's any answer that you can provide at this point. But I agree with Dr. Levy. One of my concerns has to do with how the

machine or the device will eventually be utilized. You know, you're advocating and you have data for a four-minute freeze, thaw, six-minute freeze on the other side. But your machine has a fail-safe that is after ten minutes. And you have evidence already during your clinical trial that the four-minute, six-minute freeze was not totally utilized, that some clinicians let the machine go longer, because the temperature was not low enough.

And also I've heard several times folks mention, well, you've got the freeze ball. You want to take it all the way till you're a millimeter or two from the serosa surfaces. To me, in terms of eventual approval of the machine and something that I'll bring up in the discussion, that's of concern, because it seems like there's a whole lot of different endpoints that the clinician who's eventually going to use this machine could potentially utilize. And, yes, you've got some data to show that in a non-pre-treated uterus at four and six minutes of freezing you're okay, but in a non-pre-treated uterus and a ten-minute freeze that someone might receive might not be okay. We don't know. It might be perfectly fine.

DR. DULEBA: Absolutely.

DR. BLANCO: So just -- I'm just bringing

up the point that there's some variability here, and I think what's going to happen is that there's going to be a big issue in terms of labeling and how the procedure and the how the physician is instructed to utilize the machine.

DR. DULEBA: Certainly. May I address some of those concerns, because I have also very similar thoughts about it. First, I want to point out that even when we look on the four and six-minute freeze patients, the success isn't what we expected. But beyond that, the way I would like to look at cryoablation is as we look at any surgical tool, that indeed can be misused, but the advantage of using it as a surgical tool is that it also offers, on the plus side, flexibility. And this means, for example, addressing issue of smaller uteri, which was mentioned by the Panel, that indeed if the uterus is smaller than average, freezing can be stopped sooner because of ongoing in real-time observation of the size of the ice ball. In the same way, if the uterus is particularly large or when the ice ball does not grow sufficiently, one may choose to prolong it and use clinical judgment in the same way as when you use scalpel.

DR. BLANCO: No, I know, but you're

actually making my point.

DR. DULEBA: Yes, yes.

DR. BLANCO: Because my point is not one of efficacy. My point is one of safety. So you're making the point that you think there can be variability of the physicians. Well, the point I'm trying to make is that that wasn't how the study was designed and that in the labeling of how the physicians are supposed to use it, those very issues have to be addressed.

We're going to get into discussion later on. Unless you have an answer of fact, and I think that you don't at this point, let's just keep going on there. Write it down, and during the public session we'll go with that. So I just bring that up, and I'll bring it up in the discussion again, because I think it's important for labeling in terms of physician training and physician usage of the device.

The fourth point, again, Dr. Levy, was the anesthesia, and one of the issues was mentioning that there was less anesthesia required, or less invasive anesthesia required -- I'm sorry, I forgot exactly how it was worded -- for the cryo. And one of the questions was, well, did that difference come about because of the in-office site having more cryo

patients than rollerball?

MR. MURRAY: Yes, Dave Murray, CryoGen. I'm going to ask Dr. Townsend to address this. If it's all right with the Panel, I might ask him to also address the issue of peri-operative pain and cramping so that it's a somewhat related topic and save us up and down. Thanks. Dr. Townsend?

DR. TOWNSEND: Dr. Duane Townsend, Park City, Utah. I do private practice at Park City and also in Salt Lake City. I get reimbursed for my time from the Company, and I believe I have a small interest in the Company, but I'm not positive. Sounds odd but it's true.

The question of anesthesia comes up, and I know in the studies that we were -- had the opportunity to treat the most number of patients by freezing and also by REA, and I've treated a large number of REA patients, the issue about office therapy and such -- Paul Inman, who is depicted on the video, did all his patients in the office, and his success rate was comparable to all of ours -- in the high 70's.

I can't give you the uniqueness of the Alabama results, and I've not had a chance to talk to the individual why his results were what they were,

but certainly you can do this in the office. Inman has demonstrated this. It can be done safely and effectively with minimal degree of patient discomfort. The patient you saw on the video actually was awake. And the patients that we did at LDS Hospital were done in the operating room, but they were done under conscious sedation half the time. We could converse with them. They did not complain of significant degree of pain or cramps.

Now looking at the question about do the patients with cryoablation and REA have more or less pain --

DR. BLANC0: I'm sorry, let me interrupt you for a second.

DR. TOWNSEND: I'm sorry, yes.

DR. BLANCO: Because I don't think that was Dr. Levy's question, and I think we got it answered. The question that I believe she was addressing was, was there a difference in the type of anesthesia utilized by site so that some sites that would have predominantly offered only local and non-general anesthesia do more cryo patients, okay, and therefore altered or biased the results towards cryo, quote, unquote, "needing" less general anesthesia. Am I following that up correctly, Dr. Levy?

DR. LEVY: Well, clearly, the site in Alabama, which I think was one of the Company's explanation for that low success rate was that it was an in-office or a site in which things were being done in-office. Hypothesis explanation, whatever. I think that one of the issues about doing things in-office is that you're doing them under local anesthetic. I have a real issue with the whole conservation regarding anesthesia in that it wasn't randomized, it wasn't really designed to be studied in the first place, and perhaps the cleanest thing we could possibly do with the anesthesia thing is just drop it, because I don't think that's it's clean at all, and it clearly wasn't part of the study design in the first place, and there is definite differences among sites.

DR. BLANCO: Do you understand. The issue is whether you can -- the product or the device can make a claim that they require less general anesthesia, okay? And that's the point we're getting at, that if you're going to make that claim and the study wasn't designed to make that claim, and could there have been bias by certain areas having more cryotherapy where they normally wouldn't have had general anesthesia available. Is that clear?

DR. TOWNSEND: Well, yes. All the REAs

are done under general and in my experience rarely under conduction, which is the other choice. Half the patients that we did at LDS, which is 50 were done, I believe, under conscious sedation, the issue about physicians therapy, I think, is -- I don't have an answer for that.

There are physicians in the U.S. who will do patients in their office. They're very skilled at it, and it's an individual situation. Dr. Inman is very good at it, his patients did extremely well, and he had no particular problems with that. And this is as far as I can go with it. I think the other area, Dr. Heppard also treated a large number of patients, and about half of hers, I believe, were under conscious sedation as well.

DR. BLANCO: Thank you. You were going to address an issue of pain?

DR. TOWNSEND: The issue of pain. When the patients would undergo the cryoablation, we'd ask immediately how do they feel, and the majority of patients would remark, "Well, I have a cramp." This would be called an adverse event. Invariably, this would be controlled with ibuprofen, did not require any significant degree of narcotics in my experience. The REA patients almost invariably went home with,

say, Vicadin or a strong narcotic than the so-called ibuprofens. So the degree of paint was substantially less in the cryo patients.

DR. LEVY: George?

DR. BLANCO: Yes.

DR. LEVY: I'd just give you a personal comment. I have never sent ablation patient home with REA with anything other than ibuprofen, and my patients do fine.

DR. BLANCO: Understand.

DR. TOWNSEND: I understand. Ours apparently require more pain medication.

DR. BLANCO: Well, we appreciate the opinions, but the reality is what I think we were trying to get was at the numbers from your study, and we still haven't received that. So if you guys want to try to put that together, otherwise I think our discussion of anesthesia is going to be pretty limited. Thank you, Dr. Townsend.

You had some slides, you said, that you wanted to show, Mr. Murray?

MR. MURRAY: Dave Murray, CryoGen. Yes, there was a comment earlier on about the results being unknown for patients who had protocol variations, and we wanted to address that.

DR. BLANCO: Please go on.

MR. MURRAY: Is this the -- yes, I think you can see here that the two groups that were those that were within the protocol, the four and six-minute on the left, and the protocol deviations on the right are essentially equivalent. So we were not able to detect -- and if we need to go into deeper, we can have the statisticians do so -- we were not able to detect a difference between the groups.

DR. BLANCO: All right. Great. Thank you. Were there any other questions that I left out that the Panel members had before we proceed on?

DR. D'AGOSTINO: About the randomization.

DR. BLANCO: I'm sorry?

DR. D'AGOSTINO: The question on the randomization, that do they actually have the randomization tables.

DR. BLANCO: Right. Thank you.

MR. LEWIS: Steve Lewis. Short answer, yes. A master randomization list was generated using software. The envelope treatments were assigned according to the master randomization list. It has been retained, and it's available for inspection by FDA.

DR. BLANCO: DO you know offhand whether

that run of 11 patients on the cryo was generated by the computer randomization?

MR. LEWIS: Yes, it was.

DR. BLANCO: All right. Thank you.

MR. LEWIS: You're welcome.

DR. BLANCO: Dr. Janik?

DR. JANIK: I have some questions regarding ultrasound. It seems like ultrasound's one of the key features here as far as safety, that you use it for monitoring for safety, and for efficacy in that if placement's not correct, as in the Boston group, the efficacy seems to go down.

Where I'm a little unclear is at the different sites, what kind of ultrasound situations were present? Were there ultrasonographers that were the second person? Were all of the MDs ultrasound certified? What type of ultrasound needs are there? And are there certain types of patients that can't be imaged adequately -- the obese patient, the retroverted uterus? Are you always able to see the ice ball? These seem to be some key questions in order to really say that it's safe in all circumstances. And this leads then into the training circumstance. should it be an MD ultrasound team that goes through the certification?

MR. MURRAY: Dave Murray, CryoGen. 'I just want to make one point about ultrasound at the one site that had poor outcomes. It was not the absence necessarily of a sonographer but the absence of an extra pair of hands that we believed and we hypothesized with the agency might be the case.

This was a small study, so you can't say this conclusive, but there was a succinct difference in the technique of that physician in that he used one hand to hold the ultrasound transducer and the other hand to hold the probe. And we learned later on in the study that it was important, or it appeared to be important, to maintain traction on the tenaculum as one of those intricacies of technique to make sure you stay at the fundus. Unfortunately, with only one hand he was unable to do that and actually didn't know we should be doing that early on in the study. So we think it's more an issue of number of hands. Actually, that physician, if you know it from the book, is a very skilled sonographer.

DR. BLANCO: All right.

DR. SHIRK: I don't. think he addressed Grace's other question, though, and that's basically a credentialing process and the fact that this really is a two-person procedure, not a one-person procedure.

And how should the credentialing be handled as far as -- the training as far as the sonographer physician together, because it's obvious that from what your recommendations are that you have a sonographer. And the question would be basically whose expertise are we using, the physician's expertise or the sonographer's expertise?

MR. MURRAY: I'd like to hand that question to Dr. Duleba.

DR. DULEBA: Antoni Duleba from Yale again. I can answer parts of the question. Obviously, I wasn't present at other sites, and I know only from what I heard from investigator meetings when we met towards the completion of the study and from my personal experience.

The issue indeed is that we need a third hand rather than a second person, and I had resident or a nurse holding ultrasound transducer in position, which I directed the person to, and it was more than satisfactory. However, I did need at the same time two hands to hold the uterus tenaculum attached to the cervix while at the same time positioning the probe appropriately. I don't believe that skilled sonographer is helpful, but -- I should reword it. I do believe that somebody who performs the procedure

should have understanding of sonographic pictures. If that person does not have that understanding, then they would need a second person who is skilled sonographer.

So, indeed, in either way, there's a person needed who can interpret what they see, but it doesn't require two people. It requires three hands.

DR. JANIK: So I think the key is that in the labeling, it needs to be emphasized that you need to have ultrasound ability to do this procedure.

DR. DULEBA: Yes.

DR. JANIK: And I don't think necessarily it's that emphasized in what exists. Also, are there any types of patients that can't be imaged well with this seeing the ice ball? Any technical --

DR. DULEBA: Obviously, there are variations in the quality of the image. Very obese patients present poorer quality image, but not to the extent where it would prevent one from seeing the ice front or the front of the cryozone advancement. Patients where -- we made sure that all patients had full bladder, of course, in the beginning of the procedure. In patients who did not have a full bladder, we had to insert a -- to fill up the bladder in order to create the acoustic window to adequately

see it. But I am not aware of variance of anatomy which would preclude visualization.

DR. JANIK: So placement of the probe is always possible.

DR. DULEBA: Yes.

DR. BLANCO: All right. Let's go ahead and move on, because we're really getting into a discussion, and we'll need to bring that up.

What we're going to do now is read very quickly through the discussion questions and then tackle them one by one. And I think we'll see that a lot of the issues that are being brought up now about the ultrasound we need to discuss in number 7.

All right. The first question is -- safety and effectiveness is the first area. The first question is: Design changes have been made to the device in response to malfunctions experienced during the clinical trial. Malfunction rate, 26.5 percent. Has the sponsor adequately addressed the issue of device reliability? If not, what additional studies, non-clinical or clinical, does the Panel recommend to validate the commercial design? Should the labeling incorporate information regarding failure rates or potential need for multiple units?

Number two: In the clinical protocol the

procedure was to involve one four-minute freeze and one six-minute freeze in opposite cornua of the uterus. In the clinical trial there were several instances of additional or longer freezes being performed, mostly secondary due to device malfunction. Is the standardization of the procedure, i.e. number and duration of freezes, criticalto device safety and treatment success? Should the device be designed to assist the investigator in performing only the number and duration of freezes specified in the clinical trial protocol?

Number three: There was a wide range of success rates among the clinical sites. Randomization also varied among the sites. Do you have any recommendations for training or labeling to achieve more uniform success rates?

Number four: The 12-month success rates below satisfy the sponsor's statistical hypothesis. Do these results show that the device provides clinically significant results? And we have a table which I'll let you look at, and we'll bring that up when we're discussing this specific question.

Number five: Was the incidence of adverse events in the treatment arm, e.g. pain, cramping, and bleeding, acceptable? Please comment on any

additional informationneededto betterunderstandthe adverse effects.

Under the heading of labeling, number six: IS the proposed labeling adequate? Do you have recommendations for changes or additions to the labeling -- A, user's manual, attachment F of the Panel review package, and B, patient brochure, attachment E of the Panel review package?

Training programs, number seven. Please identify aspects of physician training which you believe are important, i.e. patient selection, patient counseling, risk to pregnancy, duration, number of freezes, use of ultrasound, troubleshooting if the device malfunctions. Should there be hands on practice with a proctor for a specific number of cases? What are the specific skills necessary to successfully perform this procedure?

Post-market study, number eight? Under current FDA guidance, patients from the pivotal study are scheduled to be followed for a total of three years after the procedure -- one year pre-market, two years post-market. Is the proposed follow-up plan adequate to address issues of long-term safety and effectiveness?

Okay. Let's go back and put question

number one up on the board. Safety and effectiveness. Question number one: Design changes have been made in response to malfunctions experienced during the clinical trial. Has the sponsor adequately addressed the issue of device reliability? If not, what additional studies, clinical or non-clinical, does the Panel recommend to validate the commercial design? And should the labeling incorporate information regarding failure rates or potential need for multiple units?

Any Panel member would like to begin the discussion? Dr. Levy?

DR. LEVY: Do you have any data to show us -- once you've incorporated all these changes as time went on, do you have the last 25 or the last 50 cases that you could demonstrate to us that with these changes there's indeed been an improvement, so that we're not looking at 25 percent of the overall, but let's look at the last 50 cases or the last 30 cases, whatever you have, after all of your changes have been incorporated?

MR. MURRAY: Well, I have two parts to that answer. Dave Murray, CryoGen. We do not have 25 cases after all the changes have been made. What we do have is -- and I told you I might allude to this --

commercial experience where we look at our complaint database. We told you earlier that 16 of the 18 root causes were followed up with a corrective action, and that those corrective actions or changes in either product or process were validated. And I want to emphasize that these changes did not change the performance of the device. They have to do with changing materials used to build it to eliminate potential sources of contaminants, et cetera.

But in those 16 that have been validated, there are zero complaints from the field in our commercial experience that have any of those issues as a source. We have two root causes that we are currently in the process of validating, and we believe we should expect the same kind of result from those as we might expect from our current validation. We identified -- the clinical setting was a great place to identify issues that we certainly wish we had identified earlier, but we were able to validate and correct -- correct and validate those following that.

DR. BLANCO: Mr. Murray, what do you mean by validating. Dr. Levy is asking what data do you have that the new machine does not have the same problems? What do you mean by validation?

MR. MURRAY: We are running a validation

trial of the system. We did one earlier on that incorporated those 16 and ran at, I think, as Mr. Reu told you, for what would be estimated to be a year's life. And so this has to do with service interval. We are in the process of running a second validation, again, trying to predict service life of a system with all of those in it, and we run that under test conditions that are more severe than could be experienced in the clinical setting. We can put greater heat loads on the system, and we can force it fail earlier than it would ever fail, if it were going to fail, in a clinical setting.

DR. BLANCO: Please don't misunderstand me. You've been very responsive, and the FDA's even commented that you've been very responsive to the problems or issues. But the question still remains, in my mind, have you taken the new machines that are supposed to have the problem fixed -- and I apologize, I'm a simple guy, okay -- the new machine that have had the problems that were identified fixed and then put them out in the field and had actual clinicians use them on patients and see whether they ran into problems or not?

MR. MURRAY: We do have commercial systems in the field being --

DR. BLANCO: Okay. That doesn't answer my question, sir. Do you have the machines that were corrected, that had the errors corrected, out on the field?

MR. MURRAY: The answer is not 18. The answer is 16 of 3.8, because we do have those validated.

DR. BLANCO: Okay.

MR. MURRAY: Those have been in the field, are in the field, and no complaints. We do not have systems that have the last two issues that are currently undergoing validation in the field being tested.

DR. BLANCO: How many patients do you have that have been -- that have had the new machine utilized without complaints?

MR. MURRAY: Approximately400 procedures, not machines.

DR. BLANCO: Four hundred procedures with the new machine that you want to prove that no longer are getting the -- no longer have the problems that -- the 16 of the 18 issues.

MR. MURRAY: Right.

DR. BLANCO: Okay?

MR. MURRAY: Yes.

DR. BLANCO: What were the two issues, just for the Panel's --

MR. MURRAY: The two issues that remain are this GMC or primary source plugging issue, which Gene talked about quite a bit, Mr. Reu. And then the second one was this issue of putting an appropriate amount of thermally conductive medium in the tip of the probe so that you can easily connect it; you don't get a piston effect. And we're in the process -- we've developed procedures and processes to do those, and we're in the process of validating them.

DR. BLANCO: Dr. Levy, does that answer your question?

DR. LEVY: I think it does, yes.

DR. BLANCO: Okay.

DR. SHIRK: You're assuming that the 19 instances where the temperature probe didn't come up to minus 80 -- go to the minus'80 degree sonograde was totally due to the amount of gel that was around the unit; is that correct?

MR. MURRAY: No, that's not correct. There were a number of root causes for that. Some of them involved physician not doing a pre-cool.

DR. SHIRK: Okay. What things have you done -to solve that problem since 53 percent of those

patients were failures in that 19-patient group?

DR. BLANCO: While you're getting Dave to address that, I just want to remind the Panel members that the FDA likes for us to discuss things among ourselves and not have a dialogue back and forth with a company, but really to kind of look at the issues, and then they can go back and address those issues with a company on how they can resolve them. But go ahead, sir.

MR. REU: Gene Reu from CryoGen again. I think your question was related to what issues were presented that caused the systems issues that were observed and what we've done to correct those; is that correct?

DR. SHIRK: Correct.

MR. REU: Essentially, right now, as we had described earlier, there were a few different root causes that combined that could have produced unsatisfactory temperatures during the procedure. Those, again, as Dave Murray had alluded to, have been resolved, the 16 issues, that is. The best example of what we do to show that our system works effectively and can allow the clinician to be assured that it will work well during a procedure is that.

We have an automatic pre-cool cycle that

the system goes through. When you power up the system, it goes through some self-tests, and then they initiate this pre-cool procedure that essentially verifies and validates that the system is working effectively prior to the patient being treated. So if there is any abnormality or lack of performance in any of the subsystems of the device, then that would be brought on or it would be apparent as a result of this pre-cool part of the procedure when they start up -- initially start up and use the machine.

So that would effectively -- if any performance abnormality was observed, it would be detected by the pre-cool part of the sequence, and then the user would be effectively locked out of the procedure. So they would not be able to do a procedure if there was a performance abnormality related to the system.

DR. BLANCO: Thank you. Let me try to address the issue this way, and I'll throw up a trial balloon and see whether the Panel members want to agree with me or disagree with me. I think the point, you know, which is brought up, and I think most of the Panel members would agree, is that approving a device that has a 26.5 percent malfunction rate is probably not a very good idea.

And I think that I would throw out that what I would like to see is some clinical data with a new machine that has resolved the issues that have been identified showing that out in the field with actual patients and actual physicians that utilize this, that this isn't -- YOU know, that the malfunction rate isn't this high, okay? Because I think that's kind of unacceptable. That's my bias. Now I'm going to leave it open. We're going to discuss it among ourselves. Thank you.

DR. LEVY: I absolutely concur with you, Jorge. I think that we just need to see how it works in clinical practice. On the bench, with the engineers working on it, I know it works. And I also know you can troubleshoot anything that starts to happen before it happens. But in the hands of clinicians, that does not occur. We've already got a patient sedated or anesthetized, and I think it's our responsibility to make absolutely sure that this marketable device, not the beta device, indeed works the vast majority of the time.

DR. O'SULLIVAN: Jorge, the issue should be able to tell us. If. they have 400 of these commercially available and out of the field since they've made all these corrections, they should have

this information easily available.

DR. LEVY: If it's part of a clinical study. If it's just out there on the market and it's not being scrutinized, then we may not have that data.

DR. BLANCO: Well, I think that the point is not whether the data is there or not. I think the point is -- and again, somebody speak up if they disagree -- 1 think the point is the Panel, or at least I and Dr. Levy, would like to have the sponsor provide some hard clinical data of the machine that's going to be marketed to the FDA demonstrating that the current malfunction rate is at an acceptable level. I don't know whether anybody wants to address what that level is. I'd probably not want to put in a number. I think the FDA may have more experience with that than we do necessarily. But obviously 26 is too high, It doesn't have to be necessarily zero maybe, but 26 is too high.

Any comments? Dr. Shirk, I think you were going to make some comments.

DR. SHIRK: Well, you said it. You're using 26, but it's really higher than that, because if you add up everything that I've got, there's 19 times when it didn't go to the proper temperature. There were six cases where there were total stoppage of the

procedure. One was a perforation, and that's a physician error. But then there were like 56 out-of-the-box failures out of the thing. That comes up to a total of 81 problems with this thing. And I think 81 out of 189 procedures is higher than the 26. so I really feel fairly strongly that we've got to have some kind of a study ongoing after if we approve this that all these problems have been corrected satisfactorily for the Panel.

DR. BLANCO: Yes.. I just would like to add, Gerry, though, that -- 1 mean I don't think that the machine's responsible for physician error. So what we need to -- and this, I think, will be addressed in one of the other questions -- is the issue of perforation and what do you need to have to minimize that, rather than count that as a malfunction rate of the machine.

Any other comments? Yes, sir.

DR. NEUMAN: Yes. I would like to just address some of these things too. I think that many of the errors are -- I shouldn't say errors -- but problems are common problems in the manufacturing process. And I think that there is a reasonable approach to reliability analysis that could be used to demonstrate without actually having to have these

devices in the field, that these problems have been corrected. There are other problems, such as the thermal coupling medium issue and the automated approach to having that in the disposable unit, that again with some good laboratory data this could go a long way to convincing the FDA that in fact that issue had been addressed.

Nevertheless, the second part of the question is should there be any ongoing studies, and I think even once those kinds of things have been demonstrated that we ought to have some reliability analysis. And in particular, I'm curious about the, for want of a better term, the change the oil meter on the device and how the firm determines what is the time when that light comes on or whatever. I actually wonder how it work in my car for that matter.

(Laughter.)

But I think that's a -- it's a crucial factor. It's probably a moving target, and perhaps part of what the Company should do is to have a strategy to update that as the device is used in the field. But that's an important aspect of the reliability.

DR. SHARTS-HOPKO: My comment dovetails on Michael's. I don't see in the user's manual how many

times it's recommended that you use the probe and resterilize it. And I didn't know if the little warning light is geared toward probe recycling.

DR. LEVY: It's my understanding that you don't resterilize the probe. The only sterile piece is the disposable piece which attaches to the probe, as I understand it.

DR. BLANCO: Right.

DR. NEUMAN: And they have a feature, the so-called Dallas chip, which I have no idea what that means, but that in fact prevents you from doing that.

MS. YOUNG: Yes. I wanted clarification about that too, because I have down that there are four units, and one of the -- four pieces to this: the console, the control unit, flexline, and the cryoprobe. And only one of them is supposed to be disposable, and I still don't understand, and forgive me for not understanding this, it was explained by the sponsor that the reasons were given why the control unit needs to be disposable.

But what I don't quite understand, as you know, there's a danger of that being contaminated. The cryoprobe goes into the woman. I mean theoretically let's say could be contaminated as well. So I still don't understand what is disposable here

and what is not. And is that cryoprobe or parts of it -- can it be taken apart? Can pieces of it be sterilized and other pieces not be sterilized? I still don't understand that.

DR. BLANCO: Okay. I think there are three different issues. I think Dr. Neuman brings up the issue for the sponsor that there needs to be some sort of a system after the machine is used so many times or whatever they come up with to realize whether the gas is low or the compressor isn't doing well, as you said, whether the oil needs to be changed. So that's one issue in terms of performance of the machine that you would recommend that it be looked at in terms of long-term use out in the field.

I think, Nancy, you brought up the issue, which I think was more of you use a reusable probe and you're not supposed to reuse it, obviously. But when do you not reuse it? I mean when you talk reusing, are you saying reuse it on another patient after sterilization or whether you put it back in after you've taken it all out or do you pull it out a little bit? That means you need a new probe. And I think, actually, your question brings up a larger issue that I don't know if we want to go off here or whether we want to wait till seven on training, which is

physician labeling and physician direction, which I think was somewhat limited in what is so far put together. I'm trying to choose my words correctly here. Because as we've heard this morning, there seems to be a lot variability, I mean even to the endpoint of what you need to use, but there are issues about maybe you don't need two ultrasonography techs or a tech and another person, but you do need two people -- one to run the ultrasound and one to do the procedure and one that knows what they're looking at. so that's something that needs to be identified in the physician labeling and education and training. The whole endpoint, which endpoint, four to six minutes? Four and six minutes? Ice ball? What do you use that needs to be addressed? So there are a lot of issues on that training.

And then, Diony, your point was slightly different. You're still concerned why some of these things are disposable and therefore more costly. I don't know how much we want to get into that, and maybe other Panel members can address it. I mean that's just the way they designed it. We're not here to look at cost. We may want to address that issue, and we may want to suggest to the Company that maybe they ought to try to make it so really what needs to

be disposable or not.

But go ahead.

MS. YOUNG: No. It's just that I'm still not -- the cost issue is just one issue, but I'm still absolutely not clear about if the control unit, which doesn't go inside the woman's body, can be contaminated by the woman's body or secretions or whatever, and the cryoprobe, which does go into the woman's body, is certainly exposed to the woman's secretions or whatever, could be contaminated, one of them is disposable. But the one that is disposable is the one that I think maybe less contaminated than the one that apparently is not disposable. And if the cryoprobe is -- is that used many times and sterilized in between each usage?

DR. SCHULTZ: Could I just make one recommendation?

DR. BLANCO: Go ahead, Doctor, please.

DR. SCHULTZ: I think that there -- it sounds to me like there's still some confusion as to which parts fit in which parts and where they go. So I would like to recommend that perhaps someone from the Company could spend one more minute sort of going through all the individual parts, what constitutes the console, the tubing -- I think the console and the

tubing are pretty clear. But I think the probe and the control unit and how those fit together and what touches the body and what doesn't touch the body, I think two minutes on that might save us a lot of discussion.

DR. BLANCO: I think that would be excellent, and if you've got pictures, a picture's worth 1,000 words.

MR. MURRAY: We have pictures. I guess the first thing I'll ask you to do, we want -- is our computer still up here? Could we plug it into the projector? I might ask you to turn --

DR. BLANCO: Either that or where are they on here?

MR. MURRAY : Tab F in your Panel pack, page 149. And then we'll try to get this up on a slide here quickly too. Everybody with me?

Okay. At the very top two diagrams, there's an illustration of a box sitting on the ground, and the right hand of the assistant there on the top photo is touching a box. That box is the console. The flexline is just to the right of that person's arm, and it's that black, flexible line going up. And then if you'll look down at the third diagram down, the part that is in that person's right hand,

the gloved hand, is the disposable control unit. It has the drape backed up over it, and it is white plastic. The part that's in the other person's hand is the cryoprobe. The cryoprobe is permanently attached the device. It rests in an enclosure on the side of the device when it's not in use. But before the system can be operated, a sterile, disposable control unit needs to be put in place, and you can think of it as a sheath so that it creates a sterile barrier. That's the part that's disposable.

Here we go. If you'll look at this right here. This is the disposable control unit. We photographed it without -- there's actually a drape that goes on the back here. It doesn't photograph very well. That's the disposable control unit.

MS. YOUNG: Finally. Thank you.

DR. BLANCO: All right. I think we understand now, so I think we can move on.

MR. MURRAY: Okay.

DR. BLANCO: Okay. Thank you. All right. Now --

MR. MURRAY: May I -- do you want us to go into the other two questions you were raising?

DR. BLANCO: No. Let's move on. We're going to move on. Okay. So are we happy with that

now? Okay.

Any other comments on question one and any comments about labeling? Okay.

I guess in summary, and make sure I keep it correctly, my issue would be -- we shouldn't require labeling. We should make sure the machine works. So it shouldn't be a labeling issue. And I think in some way or form whether it's through validation, as Dr. Neuman mentioned or whatever, we need some actual data being presented to the FDA that says, hey, we fixed these problems. It's not happening out there when docs are using the machine. Fair enough? Cindy?

MS. DOMECUS: I just wanted to 'add that the Company, I think, said that they've got data on 400 patients, which I assume have been done under the 510(k) approval and not under an IDE. But if there is a way for the Company to go back and uniformly gather that data and objectify it and make it look close to a clinical trial, that those 400 patients should be looked at as a possible avenue for providing clinical data to address this, if it's possible. I don't know really what was done and how many sites are involved, but ithink that should be an option.

DR. BLANCO: All right. That would be a

recommendation, and that would be fine. I think it's just a matter of some demonstration that the rate of failure is lower than what's been reported.

All right. Anything else on question one?

All right. Let's move on to question two 'then. In the clinical protocol, the procedure was to involve one four-minute freeze and one six-minute freeze in opposite cornua of the uterus. In the clinical trial, there were several instances of additional or longer freezes being performed, mostly secondary due to device malfunction. Is the standardization of the procedure, i.e. number and duration of freezes, critical to device safety and treatment success should the device be designed to assist the investigator in performing only the number and duration of freezes specified in the clinical protocol?

Any comments to start us off? Yes, ma'am.

DR. SHARTS-HOPKO: Okay. I'm referring to page 23 of the user's manual in section F. And it's been alluded to before that clinicians using the product will exercise clinical judgment, but this talks about -- well, before this page in the user's manual there's some variability in how long you're going to leave the freezer on. But on page 23,

specifically, it gives you the option of -- end procedure? Choose no if additional freezes are required. And we don't have any information on how a clinician would determine whether or not you need to stay in longer or do a third freeze or any of those issues. And I'm concerned about that..

DR. BLANCO: All right. Any other comments? Yes, I really would like to even broaden this subject up a little bit. And this is the issue that I brought up when we were talking about what's the endpoint? I mean the endpoint that we mentioned is four to six -- a four freeze and then a six-minute freeze, but I mean we've also heard about freeze ball size and freeze ball getting to the serosa, temperature of the tip as being an issue. I think that all of the -- 1 mean there's going to be enough variability once you put it out in the field with clinicians using it, being a clinician myself, that I mean we don't need to go into it with a heck of a lot of variability into what the recommended procedure is to do this thing right.

so I think there needs to be some thought given, it doesn't need to be today, doesn't need to be today, but I think that there needs to be some thought given as to what is going to be the endpoint, clearly

documented, okay, and then dealt with FDA as to what that endpoint is and agreed to. And I think you might treat other -- if the study used a four and six, that may be what you want to do, and you may want to use the freeze ball as a safety issue of saying you don't want to have it more -- get closer to the serosa than one or two millimeters. And if you do then you need to stop the procedure. But I don't think you can -- you know, you can't say -- you can't change the target of what the endpoint is depending on what you're dealing with. Is that fair? All right. Gerry?

DR. SHIRK: Well, you know, I guess it comes down to one of the initial questions I asked when we were talking about the freeze ball thing as they chose the freezing pattern that they did. And that the logic of using a longer freeze for the second area and so I would assume that when people start using it they'll probably do a four-minute freeze, one cornua, and a four-minute freeze the other cornua, and four-minute freeze down the center, which is probably going to get you the best results, because the clinicians going to want to try and get the best results. And the question is, basically, should we force the issue into staying with the protocol and not allowing the machine any latitude to do things or is

it just sort of dealer's choice when it comes to using a machine as a clinician.

DR. BLANCO: Well, I don't think the issue is how to use the machine as a clinician, because no matter what you put down there are going to be clinicians that are going to vary. And any clinician in the audience will nod their head, I think, in agreement will vary what you do. That seems to be the nature of the beast in the country.

I think the issue is what is going to be the recommended surgery needs to be detailed and specific. And if the study used a four and six, I mean I don't see how we can all of a sudden change it. And you can talk about all the other things, but you've got to be careful about how you talk about them, either as safety issues or another way or something else, but that you still have to stick to whatever the study set up was, right? Barbara?

DR. LEVY: Jorge, I'm still very concerned about those two sites with very low success rates. And I think an analysis of the technique that those surgeons were using is really criticalto the labeling here. Clearly, something was different in those two sites. Maybe it was the tenaculum thing. Those kinds of things have to be analyzed and then put in the

labeling. I think -- you know, I'm relatively satisfied that the success rates weren't particularly different in the protocol violations versus the four to six. Nevertheless, we have to decide that four and six, because that was the way the study was designed, that's going to be the labeling. I mean that's pretty clear.

And then if the Company chooses to allow some leeway in there, for whatever reason, you've got to tell us what the reason is and what the clinical parameters are that might cause you to do that. In other words, in advising neophytes and using cryosurgery as endometrial ablation device, you can't leave that much fudge in there. Docs think they know what works and what doesn't work. Freezing the cervix is not the same as freezing the endometrium.

So I think the fudge factor's got to come out. We need to understand why those two sites had low success rates, what it was about the technique that was different in those two sites. That has to be analyzed. And then from there we can tighten up the labeling, but the labeling clearly has to be tightened up.

DR. SHIRK: But I think there's more than just the two sites that are low, Barb, if you really

look at it. I mean if you looked at five of their sites -- Yale, Denver, Los Gatos, Alabama, Boston, Mass -- and you took those all -- those were the only sites that we're using, you wouldn't meet criteria on this. I mean they're all at 70 percent or below, and if you look at their six-month data, it was even a lot worse so that from a statistical standpoint this thing seems to be very operator dependent as to what the success of the procedure's going to be.

DR. LEVY: And that's what I really think needs to be analyzed. I think it's incumbent upon us, as representatives of the FDA, to try to sort that out and figure out what it is. But I'm very concerned that with current labeling, under current conditions, in broad usage, the success rates with this thing might be ten or 15 or 20 percent. They may not be very good at all.

DR. BLANCO: Well, and that brings up the other issue, I think. Both you and Dr. Shirk made good points. I mean it brings up the other issue that there may be a training problem, that there may be something that certain sites did to have the higher success rate because they're more familiar with the machine or just serendipitous or whatever.

And one of the things -- so I guess we

might as well talk a little bit about that now since everything seems to be going back to doing on that. I think the physician labeling, the physician direction needs to be significantly expanded to include some of these issues -- the ultrasound issue, the training issue -- and some analysis needs to be made whether the technique and training issues -- you mentioned in the proposal ten -- that there was a learning curve of ten. Well, even that needs to be addressed. How many does it take to get the procedure right before you know that you're going to get higher success rates? And there may be other issues, but I think there's a lot of information for a physician training that isn't in --

DR. LEVY: Yes. And what are you going to tell those first ten patients?

DR. BLANCO: Well, maybe they have to be done in conjunction with someone else. I don't want to put that into the requirement at this point just yet, but I think that those are all issues that the Company needs to address in terms of its labeling for the physicians and in terms of training.

All right. Over here.

DR. D'AGOSTINO: Did the data actually show that after the first ten the success rates

improved drastically?

DR. BLANCO: They say that, but I don't know that they showed that.

DR. O'SULLIVAN: But there's certainly no question when you look at the data and did the highest numbers, that they did have the highest successes.

DR. D'AGOSTINO: Well, they could have started right off with the highest successes.

DR. O'SULLIVAN: This is true.

DR. D'AGOSTINO: You know, in the sort of drug arena where you require two studies, you oftentimes see the first study is a smashing success and the second study is a smashing failure. And it's because of the broader range of investigators. And it isn't necessarily the case that you can handle that by telling how to -- improving the label and so forth. So I think they do have some demonstration along the way that's necessary.

DR. O'SULLIVAN: What may be useful, though, is -- and I think if you take this information and look at what I said about the institutions with the four -- especially the four and perhaps the five highest number, that it probably does point out that there needs to be some kind of education and proctorship of some sort, perhaps, before going right

into this instead of just doing it.

DR. DIAMOND: Jorge, perhaps Dr. Kotz could make a comment about whether they got better with experience, because one of the things that we were given to read, which didn't mention that if you excluded those sites that had very few cases -- I'm assuming you wrote this -- that if you only look at those sites that had lots of cases, there was no learner's curve. It's only if you include the sites that had very few cases that a learner curve was evident.

MR. KOTZ: Yes, I can address that, yes. I'm Richard Kotz, statistician for the FDA. I analyzed that issue, and I did find -- I believe that the model that they used --

DR. BLANCO: I'm sorry. Let's stay together, guys. Okay, go ahead.

MR. KOTZ: I believe that the model the sponsor used to look at that issue included all sites. So you're including several sites with a few number of patients, approximately ten, who had poor results. You're including that to analyze this whole issue. So that brings down the rate of the first ten overall. So if you look at just the sites with a sufficient number of patients, you don't get a statistically

significant improvement after the first ten. It does look a little bit better but nothing that can be statistically supported.

DR. BLANCO: So what you're saying is that the two sites that had the very low success rates had, I think, very low patients.

MR. KOTZ: Yes.

DR. BLANCO: And that those are what's bringing down those early first ten.

MR. KOTZ: Right. There are actually three or four sites like that with very few patients, yes.

DR. BLANCO: Okay.

DR. D'AGOSTINO: Again, if you do sort out the sites that had more than ten, from what I just heard, that you don't really have a smashing statistical proof that there's a learning --

MR. KOTZ: Correct.

DR. D'AGOSTINO: -- that's going on.

DR. BLANCO: But then in fairness to the Company, what that says, basically, is that maybe you don't need to have all this training, but you still need to analyze why these sites -- I mean the numbers are so different.

DR. D'AGOSTINO: That's what I was trying

to say. I think there may be something else. Training is obviously useful, but there may be other things.

DR. BLANCO: Okay. I think Diony was first here.

MS. YOUNG: Yes. Relative to the success rates of the sites and what might be the factors involved, one of the issues that is -- one of the factors that appears to be different in the pre-treatment protocol is the option of thinning the uterus -- thinning the endometrium or not. And I was unable to sort of gather in places -- it's optional in the informed consent, which we just got today, protocol. It was a recommendation that physicians do it. In the patient brochure, it is optional, and patients are told that your physician may use this thinning agent for the endometrium.

And I suppose that in the studies, in the different sites, maybe in some of the sites the endometrium had the thinning agent and maybe in other sites they didn't have the thinning agent. And I would like to ask if thinning the endometrium could be a factor in the success of the procedure?

DR. BLANCO: I think, if I could make it broader, I think everybody's in agreement on the Panel

that the data needs to be analyzed to try to find out why these sites have such a markedly different success rate and try to address the issues of what went on at those sites that resulted in that as opposed to the other sites to be able to identify if there is a problem that needs to be addressed through labeling or changing the device or whatever. Is that fair enough? I mean I'm making it broader, not just the use of the Lupron, but I think that the other things that may need to be looked at, whatever data they have, to see why they were different.

DR. JANIK: I think they were all Lupron pre-treated in the protocol. So that's not it.

DR. BLANCO: Yes. So that isn't it.

DR. JANIK: The only thing that -- well, maybe there's others, but the ultrasound question to me still isn't very clear. Are all these sites all ultrasound trained? Is the ability the same in all? Is the placement the same? It seems just from clinical experience to be a wide variation in GYN is their scanning ability.

DR. LEVY: And I was going to comment. The other issue is the skill and level of endometrial ablation experience in general. Just from my own personal knowledge, I know some of these sites have a

vast experience of endometrial ablation; others, less so. Even though this is a non-hysteroscopic technique, it may be that the training and experience level of the operator in terms of endometrial ablation overall made a big difference.

DR. BLANCO: All right. Any other comments? Yes, we kind of moved on into number three. So let's go back to number two. Any other issues that the Panel would like to address on number two?

DR. LEVY: Jorge, I'd just like to say the second part of that question, should the device be designed to assist the investigator in performing the number and duration, I would say that stuff needs to get cleaned up. Why it should be allowed to be on for ten minutes if we're only recommending six minutes, that doesn't make good sense. And I think between the sponsor and FDA that piece of it needs to be cleaned up. If there are going to be clinical circumstances in which ten minutes is required for some reason, then it may make sense to have it the way it is.

Secondly, if you've determined that tenaculum pressure is necessary for appropriate placement of this device, then perhaps having-a hook or something else on there to provide that tenaculum pressure may be something that would aid the clinician

in doing this properly to get the kind of outcomes that you want to get. But I think that clearly the second part of this question needs to be addressed, and I don't think we can addre'ss it until we've cleaned up the fuzzy part of operator decisionmaking.

DR. BLANCO: Dr. Diamond?

DR. DIAMOND: I want to start off by saying that I think in the long run there needs to be a definitive protocol by which a success is going to be defined, whether that's amount of time or an ice ball or whatever. Having said that, though, uteruses vary in size and shape and thicknesses, cornua uteruses, which physicians may not necessarily recognize ahead of time unless they've had a reason to evaluate the uterine cavity or other abnormalities that may be present. And so I think there is a value in physicians being able to modify how they are applying treatments.

And I would not like to see it where the device can only be used in one way for once at a time. I think that having that variation I think is valuable, just like we have certain ways we use our lasers, our electrosurgical generators, but yet we have a range of ways in which we can use them.

Furthermore, it would be my hope that

perhaps this device might be able to be used in other locations throughout the body at some point in time. And rather than having to have an OR which is cluttered with one instrument which can only be used for this purpose and one for the cervix and one for each other site, I'd rather be able to see them be used different ways, although setting them at for what is supposed to be the endpoint that is desired, as identified by the Company.

DR. BLANCO: Okay. Any comments on that? I have a comment. How about some sort of a compromise? I agree with you that there needs to be some variability, but I think also what some of the Panel members are bringing up is -- you know, we don't have a lot of evidence from the thermal study looking at the temperature variations in the uterus. I mean there were a few number of patients in very specific settings there and again without the thinning of the endometrium.

Would you like to see a small number of patients where that kind of data is reproduced, maybe letting the freeze go more to the ten minute maximum that they currently have to at least address the issue of safety or if somebody doesn't realize or doesn't see the ice ball and just keeps freezing until the

machines shuts itself off?

DR. DIAMOND: Yes. I would absolutely like to see that. I also would like to see the effect of, I call it, the Heppard modification, which it points to the cornua and then pulls it back, because I don't see that described any-place in the protocols. It makes a lot of sense, but yet that's not what has been described as being done. So what is the effect of that modification on being able to treat those areas around the temperatures that you've achieved in the cornua?

DR. BLANCO: And I think that addresses the issue that keeps recurring, which seems to be a big issue, which is that even in the study and in the suggestions there seems to be a lot of variability. And at least we know there's going to variability introduced by the physicians. At least when the machine goes -- the device goes out and it has a way of doing things, it ought to have a clear, one way, this is how we recommend you do it. Fair?

Okay. Any other questions? Comments? Mike?

DR. NEUMAN: Now this is just a very simple question. I'm approaching the time in life when it's hard to keep something in mind for two

minutes.

(Laughter.)

I'm wondering if having the machine instead of beep every two minutes give some other indication so you know actually how far along into the procedure you've gone?

DR. BLANCO: So you're suggesting like, what, that it -- some sort of a number, you know, two minutes, four minutes, six minutes, something like that?

DR. NEUMAN: Whatever. I mean I just think it's difficult if' you haven't been paying attention and the thing beeps. I mean really what you should do when it beeps is look at the little blue screen, but if the beep could be a little more informative, it might be more valuable.

DR. BLANCO: Okay. All right. Anybody else, any comments? All right. Anything else? Okay. I think we probably addressed some of the issues in number two.

Now, number three, we've kind of talked a little bit about, but let's go over it again. There's a wide range of success rates among the clinical sites. Randomization also varied among the sites. Do you have any recommendations for training or labeling

to achieve more uniform success rates?

Well, on the issue of randomization, we've been told that that's just the way the computer put it out, so I guess the only issue would be that the FDA -- they need to provide the data to the FDA to show that, and that would be fine.

As to recommendations for training or labeling to achieve more uniform success rates?

DR. LEVY: I think that the sponsor and the FDA have to get together and figure out what those issues are. Certainly, pulling back from the cornua, putting traction on the tenaculum, I mean you've identified a couple of them, and those things need to be incorporated into the training in some uniform and reliable way. Granted that clinicians are uniform and reliable, but the whole concept of globalization devices is that they're supposed to be easier to use than hysteroscopic devices. And I think in order for us to do that, it's going to have to be very, very clearly spelled out exactly what the technique is. And that has to be the labeling as well.

DR. BLANCO: Go ahead.

DR. SHIRK: I think one of the big issues, and I still sort of disagree with the Company as far as a learning curve, because if you go back to the

six-month data, it really doesn't -- and look at those sites that were -- all the sites that -- the two that had -- you know, only ten sites were -- one was at 80 percent; the other one was at 50 percent. The other two had 15 patients, and they were still low, and they were the two low sites. So I mean they were -- they hadn't improved over the last five patients, so they were still pretty much the low sites.

so something's going on other than learning curve as far as technique. And I think those things need to be identified before you can identify it with labeling. I think it's certainly something in the technique that's important that needs to be identified and the labeling needs to go back and identify this, or the training needs to, but I think it's beyond learning curve.

DR. BLANCO: Well, I think the data on the idea of the learning curve probably has been put to rest also with the statistical issue of the smaller sites were the ones that had worse successes. So that's probably what we're seeing more than anything else.

I think the issue you bring up more generally is that it's very difficult to be able to make suggestions on recommendations on what needs to

happen without an analysis of what that variability was and what they were doing at different sites. I mean I don't know what they were doing at some of these sites, but to go from a very high -- I'm trying to look and see the two highest numbers of success rates -- from 25 to 90 in two different hands, somebody was doing something different. And I don't know what it is, and I don't know if we're going to find out here at the Panel meeting, but that needs to be looked at, and some attempt needs to be made to see what was the difference in the procedure or the technique or whatever to try to standardize it a little bit more and avoid the lower rates.

Diony?

MR. YOUNG: Yes. I want to raise the thinning of the endometrium again. If this was used in the study in all of the sites, then why is it considered to be sort of optional in some of the other material that we have read? I think that it should be very clear in the labeling. I mean if it's considered to be beneficial in fact to use the thinning agent for all patients to thin the endometrium, then it should be clearly stated in the labeling and not indicated that this is a sort of optional thing for physicians to use. And women in the patient brochure shouldn't

be told, you know, your doctor may do this or he may not. Then the woman is going to wonder, well, why is my doctor not doing this thing which may benefit me.

DR. BLANCO: So since the data was with the thinned out endometrium, that should be the procedure on the labeling, both for patient manual and physician recommendation.

DR. LEVY: There is no way that we can talk about success rates in any other environment. So we just can't publish anything. We have no data on anything other than pre-treated uteri.

DR. BLANCO: Okay. Dr. Diamond?

DR. DIAMOND: Jorge, I want to make one point. First of all, several times now people have made the comments that what was different in the surgeries at one site versus another. Maybe it's the patients.

DR. LEVY: The patients.

DR. DIAMOND: For example, as I understand the protocol with all the amendments, fibroids ended up being not an exclusion criteria -- polyps, that apparently it varied during the protocol. So that's one thing.

The weight of individual patients. While it may not have varied between the two study arms, it

may have varied as far as success and the amount of endogenous estrogens that are being produced and the effects on the endometrium. So there could be endogenous patient characteristics which could also be affecting those success rates of the different centers based on the referral practice of whatever they happen to have.

DR. BLANCO: Right. And they should be able to gather that data. Because, actually, when you're talking about no difference, you're really talking about the ones that were in the cryo versus the ones that were in the rollerball. And what we really are looking is the difference --

DR. DIAMOND: Within the cryo.

DR. BLANCO: Right.

DR. DIAMOND: The point I want to make, and I'm not sure if it falls here, but I'm not really sure where it does fall --

DR. BLANCO: Well, we're going everywhere, so you might as well.

(Laughter.)

DR. DIAMOND: Thank you. When we put together the guidance doctrine -- I know Barbara and yourself were on the Panel at that point; I don't know if anyone else was -- the PBAC scoring system, which

no one has really described here today, actually is a very interesting system in that it's not linear. The more you have it exponentially almost increases the amount of scoring. We had actually come up with other ways of assessing outcomes as potential endpoints, which included amenorrhea or other endpoints. And the Company very rightfully chose the one they wanted to use and would agree with the FDA, so I'm not finding fault with that at all. We gave lots of options at that point.

But if you look at the data, page 54 of our books, and if I look at the six-month data for cryosurgery versus rollerball, which is the last time for which we have the complete data, as I understand it -- because the 12 months, as I understand it are like 21 pages that are still outstanding -- total amenorrhea, cryosurgerywas 22 percent; rollerballwas 51 percent. And menorrhagic scores above 100, the opposite side are 21 percent with cryosurgery; ten percent of rollerball.

So while a PBAC score of less than 75 we're not seeing differences, if you break it out on more than a two-point scale -- what they've got here is a five-point scale -- it does look like there are differences, particularly at the extremes. And so I

just wanted to point that out to everybody and make sure people were aware of it as we talk about success at difference places, because depending on how we define it, you may come up with different observations.

DR. BLANCO: Well, Michael, continue with your thought. I mean do you think that that kind of difference is sufficient to give you concern as to whether the device is equivalent to rollerball or not?

DR. DIAMOND: I mean to go from six months to 12 months, some of those extreme differences decrease in magnitude. The ones with total menorrhagia still has a score of 100. It's now down to 12 percent versus seven percent. So it's still almost double, but my bet if you give statistics that wouldn't be significant. But the amenorrhea is 30 percent versus 54 percent. And so depending on what a woman is desiring, total absence of. menses or reduction of amount of bleeding, she may find differences in success with these different forms of therapy.

DR. BLANCO: Dr. Schultz?

DR. SCHULTZ: If I could just make one quick comment, just on the comment that you made, Dr. Blanco. Let me just make sure we understand the

device does not have to be equivalent to rollerball. The question is, I think, based on what Dr. Diamond was saying, is in writing the label and in writing the summary of safety and effectiveness, are there additionalways of presenting the data which should be included in addition to simply stating the PBAC scores at one year? So that's -- 1 just want to clarify that that's really the question that should be addressed as opposed to the issue of equivalence. Thank you.

DR. BLANCO: Thank you.

DR. LEVY: And I think, to just follow along that, I have no issue with looking at amenorrhea rates. I don't think we need to do that. The labeling for this device should clearly be its purpose is to reduce menstrual flow, just to make it simple and make it easy. And then when we look at effectiveness, the effectiveness of this device was to reduce menstrual flow below a level that's considered acceptable. That 75 score we know is an acceptable level for women. It won't reduce their blood count and those kinds of things. So the labeling should just be in very clear language that the purpose of the device is to reduce menstrual flow, not to eliminate it, not to ablate it, to reduce it.

DR. SHIRK: The question is are we

launching into number four or are we going to close on number three here?

DR. BLANCO: All right. Well, anything else that we want to add to number three? Then I'll take that opportunity to say it. You want to add something to number three?

DR. SHIRK: But my recommendations would be that I think there has to be some labeling regarding that, but I think it's got to be -- I don't think the definitions or what's causing it are immediately apparent to the Panel, and I think that that needs to be addressed by the Company and the FDA . and those labelings undertaken between the two of them. I don't think the Panel has enough information at this point to make a recommendation.

DR. BLANCO: And on that, we'll move on to number four.

DR. SHIRK: Okay.

DR. BLANCO: Unless anybody else has a comment on three, but I think that closed it out pretty well. All right.

Well, let's move on to four. So four: The 12-month success rates satisfy the sponsor's statistical analysis. Do these results show that the device provides clinically significant results? Dr.

Shirk?

DR. SHIRK: Well, I think I guess I've got several questions about the data. And I guess one of the biggest questions I've got about the data is what's unique about this procedure? If you look at the six-month data on the rollerballs, it's consistent. Generally, six months on any endometrial ablation procedure is the best you're going to do. If you look at the statistics, there's a five percent jump in statistical significance in the cryo unit thing. Some of the investigators had even higher jumps than that, as far as their statistical endpoint, over from six months to 12 months. And I guess, I don't know what the Panel feels, but maybe you guys feel comfortable with this, but I really have a question as to what's unique about this procedure that we don't know that makes the statistics on this thing keep getting better rather than worse after six months? Six months is 69.1 percent; at 12 months, it's 74 percent.

DR. KATZ: Doing the paired comparisons, I'm just looking at them, I'm seeing some going up and some going down. So before we jump to conclusions, 79, 82, 84, 82, 72, 88.

DR. SHIRK: Okay. But look at all the

rollerballs. They all stay fairly consistent, okay? I mean, basically, you're looking at basically 72, 87 on Columbia Rose; you're looking on Swedish, 79, 92.5; on Denver, you're going from 58.3 to 72.6; on Los Gatos, from 50 percent to 71.4. I mean those are --

DR. KATZ: There's loss to follow up there too. Yes, there's a loss to follow up there. There's a drop there too.

MS. DOMECUS: Dr. Shirk, I think what happened -- maybe the Company correct me if I'm wrong -- I think that some patients that missed their six-month follow up were then included in the la-month . follow up. Because I noted the same thing when I was reviewing that looked like the scores got better between six and 12 months, and that seemed peculiar, as you were pointing out. But I think that was the explanation, but I'm not sure.

DR. BLANCO: Well, I would bring up it's a five percent difference, which is small. I don't know if that's a really a statistically significant difference, number one. Number two, if you do look at the bigger sites, they pretty much stay the same. And there are differences in the numbers that will change the percentage that may be due to follow up. so I don't know -- plus there **may** be some reason why the

machine does better. I don't know whether maybe the women are having extra secretions because of some particular effects of the cryo. So I don't know that I'm that worried.

DR. D'AGOSTINO: Some of the failures are probably dropping out also from the six months to the 12 months. The numbers go down from the 12 months. So it isn't that the procedure's improving. Those who didn't get success have dropped the study.

DR. LEVY: But to answer the question that were asked, if the PBAC drops from over 150 to less than 75, yes, that's clinically significant. I mean that's the question we're being asked right now. And, yes, that's a clinically significant difference. No, it's not amenorrhea, but, yes, that's a clinically significant outcome.

DR. BLANCO: Either one of you go.

DR. KATZ: It may be the same question. Something that was brought up by Richard Kotz, the way we're interpreting the data is we're just pooling all the results to calculate these percentages. And I think that you raised the question, which came to my mind as well, and that is, is there any way to look at the success rate and sort of normalize by site rather than just pooling everything together, whether this is

smoothing over something and so we're kind of missing the true success rate. Because we did see a range of values to the rollerball, not just for the cryoprobe. I mean this will tend to smooth things out, and are we losing -- and you raised this question in some comments that you gave us, right?

MR. KOTZ: Maybe indirectly. There are ways of --

DR. BLANCO: Identify yourself again.

MR. KOTZ: Richard Kotz, statistician for the FDA. There are statistical methods for weighting sites according to the number of patients. That would possibly adjust for these rates. But, generally, and the labeling is probably the most important issue in this case, we do pool all patients together, giving each patient equal weight in the labeling. And we based our labeling on observed rates. So that's, I guess, a simple answer to your question.

And as far as the other question goes, the difference between success rates, six months and 12 months, I looked at that pretty carefully. There are a few instances where failures did become successes. There are several instances, maybe four of them, where you have noticeably very high scores becoming successes -- One rollerball and I believe three or

four cryopatients. And when I talk about noticeable, I'm talking about 250 or 500, in one case 1,000 at six months that does become a success at 12 months. I have no answers for that.

DR. BLANCO: Let me -- in the interest of time, let me cut you short, because I'm going to -- you know, I've been coming to these since 1994, I believe. And one of the things that has happened is that we sort of place a moving target for industry in terms of what is required of them from when they first come to when they don't. So I'm going to go in with Dr. Levy on this.

The industry -- I mean the Company met the criteria that was given to them to meet to win approval in terms of success rate. And so I think that's the answer to your -- to question four. They did what was asked of them to show that it works, and that's what we ought to say. I think it probably behooves the Company -- just as an aside for them, it probably behooves them to find out what the heck happened at those rates that are 43 and 25 percent, just because it's going to make the machine look better, the device look better, if there was something that happened that can be explained and looked at and studied. But I think they met the criteria.

Go ahead. Shoot that down.

DR. D'AGOSTINO: Actually, I wanted to say pretty much the same. It's not only that we agree with the endpoint, but it's within the 20 percent and so forth has been met. And even if my calculations are correct, even if the remaining 21 individuals, when the data finally comes in, it's not going to -- and they were all failures on the cryo, it's not going to change within that 20 percent.

DR. BLANCO: So I think that probably answers the question four. Gerry, any view? Anything else?

DR. SHIRK: The statisticians say roll.

(Laughter.)

DR. BLANCO: All right. Then we're rolling on.

Number five: Was the incidence of adverse events in the treatment arm, e.g. pain, cramping, and bleeding, acceptable? Please comment on any additional information needed to better understand the adverse events.

DR. LEVY: I really had no problem with the adverse events. I think one of the nice things about this is it demonstrated that there are significant adverse events for the standard procedure,

including hyponatremia fluid overflow. And so I had no problem with the adverse events in this trial.

DR. BLANCO: Any other comment? Well, the only thing I would do, I mean I think we've often seen procedures or devices that improve or lower the types of serious adverse events that can happen at the cost of maybe a little bit of extra pain. And I'm not trying to minimize anybody's pain that has any type of procedure, but it's better than hyponatremia or fluid overload and everything else. I think the issue that a manufacturer probably needs to address here is the labeling and documentation so that there is an expectation of the patient that reflects not just the serious expected --

DR. LEVY: Right.

DR. BLANCO: -- adverse effects but that a significant number of the patients will have some level of pain. And I don't know whether it was quantitated or not, I apologize. Maybe I should have read it and would have found it, but I don't remember that, some quantitation as to what adjective you can put with that level of pain. But there will be some pain to be expected and treated for that.

DR. LEVY: Right.

DR. BLANCO: Is that fair enough?

DR.' LEVY: Yes.

DR. BLANCO: Okay. Anything -- Diony?

MR. YOUNG: Yes. This isn't an adverse event, but I didn't know when to bring it up. Somewhere in the material it was noted that I think four patients withdrew their consent to take part in the study. And I would like to know why they withdrew their consent? I'm sorry, I can't find the page right now. I just wondered why? I mean all of the others were loss to follow up, but then four withdrew their consent.

DR. BLANCO: Yes, I don't know. They're looking at me like they don't know the answer, so maybe they can take a look at that. I don't know -- three? Do you know the -- 1 mean come to the microphone, if you would.

DR. HEPPARD: Dr. Martha Heppard. There were three patients who withdrew their consent.

DR. BLANCO: Do you know the reasons why, since you're up there?

DR. HEPPARD: I do not know the reason why, but I know it was not a significant issue. But I don't know.

DR. BLANCO: Okay. And I'd like to point out, Diony, that whenever -- I've done a lot of

research projects, and when you do research projects, people will change their mind for, you know -- you don't know. You don't necessarily know why. Oh, you do have the information? Please.

MS. SHEA: Cheryl Shea, CryoGen. The ladies just changed their mind. After going and talking about with their husband, they just decided they didn't want to participate. I mean that was one. Another one, she was leaving the area. She decided she couldn't participate. The third one, I don't specifically remember. They just decided for one reason or another that they did not want to participate.

DR. BLANCO: Yes. I'm not great on math, but I think it's like a two percent change. 'That's really not, in my experience, just in doing research projects, that's not that unusual.

All right. Anything else on number five? We're just trucking.

DR. LEVY: Yes, but now we're going to get bogged down.

DR. BLANCO: Okay. All right. Next one is labeling, number six, and we've kind of already done some work on this. And I think, actually, if I can just make a general statement. I think this is a

major issue. I think that the labeling and the physician labeling, physician instructions have a lot of work from just what was in here that we read.

And then there's some issues, I think, -with the patient. We brought in the issue of the thinning of the endometrium, some mention of the amenorrhea, PBAC score over 100, or the fact that this does not -- this meets the criteria for lowering your bleeding but not necessarily amenorrhea. The labeling of the pain issue. Any others that come to mind? Diony?

MR. YOUNG: Yes. Just some minor ones with respect to the patient brochure. Just a question of the reading level, a few words that I noticed that I think could be considered to be more complicated than they need to be, such as "efficacious" and "alleviate" were a couple. So just to look at that. There's a misspelling of the word "hemorrhage."

And just the other thing, the importance, I think, of making sure that the information in the patient brochure, when the labeling is changed for the user's manual, that the information in the patient brochure matches the information in the user's manual.

I think that those were the -- oh, no, there was just one other thing that I suggested --

that I even noted that I think that the sponsor could consider. There's a page in the patient brochure on 122 with illustrations, but nothing is labeled, and I think that it would be helpful, at least to -- I mean maybe it's sort of simplistic to say that the cervix should be labeled "cervix," the uterus should be labeled "uterus," and so on. But I think that when these body parts are being referred to in the patient brochure and you have an illustration, it would be a good idea to have some of the basic parts of the female anatomy. And then when the -- two of the illustrations have got a probe in them, and that could be identified as the cryoprobe.

DR. BLANCO: Dr. Janik?

DR. JANIK: In the patient brochure, I don't see any mention of doing a pre-hysteroscopy or sonography. It's present in the physician manual but not in the patient. The only comment is to do a D&C as a first surgical procedure. So I think that should be added.

Also, in the first page, it says cryoablation, to ablate or remove tissue. It really isn't a removal. It's a destruction. I don't know if that's a misleading word. That's my only two comments on the patient side.

DR. BLANCO: Any other comments?

DR. O'SULLIVAN: Jorge?

DR. BLANCO: Dr. O'Sullivan?

DR. O'SULLIVAN: Yes, I have two comments. On the first page -- I have three, actually, three comments.. On the first page, 121, where it says, "Your doctor may choose to give you medication to thin your uterus," I mean since the medication that was utilized was Lupron, it should say that that's what it is, unless somebody wants to say that there are other ones that work equally as well. But it should say that.

And they already had such a patient in this study, at least I saw it someplace, that a patient who did get pregnant because she didn't pay attention, so-called. It says here, "If you are not pregnant and don't plan to have children."- You know, we are in a changing time where women at 50 and 60 are deciding to have children. So I would suggest that this change, that "If you are not pregnant and don't ever plan to have children." And it should be repeated in several different places, because women change their mind. And when, you know, you're having sex, you're not thinking that way.

And, finally, on page 122, which is the

first time -- the second time you mention or quote a patient, it says, "The First Option procedure was painless. I've had not a period since." That is not exactly true, that it was painless, number one. And not everybody did not have a period since. In fact, the number is really equal.

DR. BLANCO: And I was going to address --

DR. O'SULLIVAN: I think there's a problem there.

DR. BLANCO: On 121, and they're quoting patients, so I'm sure it was true for that patient, and the one on 121, it was also true that it was painless. But I think that may be-not consistent with the findings of the overall study. Okay?

DR. O'SULLIVAN: No, this is clearly trying to make the patient to go for it.

DR. LEVY: I think it's misleading.

DR. BLANCO: Okay.

DR. O'SULLIVAN: Very misleading.

DR. LEVY: And I think to quote patients who have amenorrhea is misleading and not appropriate in the patient brochure all.

DR. O'SULLIVAN: That's right.

DR. LEVY: I don't think that amenorrhea, except as a complication -- 1 mean a patient should be

told that she may not have a period subsequent to a procedure like this, but I think the data for this device do not support a patient brochure that touts the possibility of not -- or the probability of both painlessness and not having a period. I think this whole thing needs to be rewritten, because it's really pushing a patient to do something whose results are not documented by the data.

DR. BLANCO: Okay. Everybody wants to talk, so let's just start over here.

DR. SHARTS-HOPKO: Okay. This may be a broader issue, and it may not be appropriate to this particular patient labeling, but ACOG has standards for decisionmaking, from most conservative treatment to hysterectomy in the case of abnormal uterine bleeding. And the first thing to consider is hormonal intervention. So I think that while it is presented as an option, it's not listed under who's probably qualified for this procedure, and I don't know if it's in our domain to say that it ought to be.

DR. BLANCO: All right. That's not where I thought you were going. I'm not sure I understand what you would like. What.was you concern?

DR. SHARTS-HOPKO: Well, my concern is that among the people who -- are you a candidate --

oh, candidate is spelled wrong, I just noticed too -- but are you a candidate --

DR. BLANCO: What page are you on, Nancy?

DR. SHARTS-HOPKO: Page 121 in the stamped-on pages at the bottom.

DR. BLANCO: Right. Okay.

DR. SHARTS-HOPKO: Okay.

DR. BLANCO: Okay, I see. All right. Go ahead.

DR. SHARTS-HOPKO: Are you a candidate? Wouldn't you first have to fail out of hormonal treatment or wouldn't that be desirable?

DR. BLANCO: Well, I don't think that everybody -- 1 see Dr. Levy shaking her head no -- not everybody, but I think most likely that's going to be the way it's going to happen. But Barbara, do you want to address that?

DR. LEVY: The way these patient brochures are used, it's in conjunction with a clinical encounter. I mean this isn't -- I wouldn't want to see this in a magazine, for example. But as a brochure to be used in conjunction with a physician's advice, endometrial ablation or destruction of tissue is an option for the treatment for abnormal uterine bleeding. There are quite a few patients who are not

candidates for medical management --

DR. SHARTS-HOPKO: Right.

DR. LEVY:. -- for one reason or another. They don't necessarily have to have failed it. So just like when I hand a patient a brochure for an IUD or for something else, that's within the context of the clinical interaction.

On the other hand, sometimes these things are used in the lay press --

DR. SHARTS-HOPKO: Right.

DR. LEVY: -- for magazine advertisements, other things. And I think the standard for what should be in an advertisement for the lay press is different than the standard for what we need to have in a patient brochure to be in the clinical context.

DR. O'SULLIVAN: Even the name, First Option, is a little bit misleading.

DR. BLANCO: Well, I'm glad -- that's where I thought you were going, because I was going to bring that up. I'm not terribly happy about the name First Option. I don't know what influence we may or may not have, but -- it's nice, but it really isn't -- this isn't -- on most patients this would not be the first option that would be used for this. So I would just throw that out.

Okay. Any other comments? Oh, yes. All right. We'll start on this side.

DR. DIAMOND: Again, page 121, where it talks about thinning a uterus, really I think in these cases the medication being given to thin the endometrium or the lining of the uterus as opposed to the whole uterus itself.

Also the question was brought up about using Lupron. My bet is when this trial started only the agonists were available in this country. Now, with the antagonists available, my bet is that they may become the treatment of choice for thinning the endometrium and that you'll have a greater length of -- you won't have an agonistic component. So I would not probably prefer to see a specific medication listed.

DR. BLANCO: I think there is just -- for the FDA's benefit, there was a lot of agreement that I heard over here, in case it didn't go over on the microphone. All right.

Comments over here? All right, good.

DR. SHIRK: On page 124, it says, "Clinical data to date for cryoablation has shown that less than eight percent of patients may be required to do additional treatment." You've got over a 12

percent failure rate. I don't know where you came up with the number of eight percent or how that's relevant, but certainly with your failure rate being 12 percent, 12 percent would at least be a number that you would have to put down, and it would probably be higher than that. So I think that that statement probably needs to be erased or --

DR. LEVY: And to piggyback on that, Gerry, just if I could, what you're really commenting on is repeat surgical management. And in fact many patients may still require medical management in addition to this ablation procedure. So I think it's misleading, because in our minds we know what we're talking about when we talk about additional treatment. But to a patient, medication, having to take a pill is additional treatment. So I think that whole statement is misleading.

DR. BLANCO: Yes. Not only that, if you look at -- this is one of the points I was going to make -- and if you look at 125 when you talk about other techniques, you quote the 85 percent success rate, okay? So I think you need to be consistent in what rates you're quoting. to folks and not in one place quote the resurgery rate and in the other quote the failure rate.

All right. Well, let's have Cindy. She hasn't said as much as Diony, so we'll give you a chance.

MS. DOMECUS: A few comments on page 120 of the patient brochure. It says, "This cryosurgical procedure represents a more convenient, cost-effective, and clinically efficacious alternative to traditional treatments." And that to me is a claim of superiority, and the study designed and the data, I think, support equivalence not superiority.

On page 125, in the quick summary here, it says, "Minimal or no need for general anesthesia." I think about half of the patients still require general anesthesia, so I think that's misleading to say minimal or no general anesthesia.

And also it says, "A fast recovery, usually only a day," and I didn't see any data in the PMA on recovery times. Maybe it exists, but I didn't see it in 'the PMA. so I think that's an overstatement, or at least not based on data at this point.

DR. BLANCO: All right. Diony?

MR. YOUNG: Yes. Also on page 125, it says that 95 percent of patients report satisfaction in the overall results. I recall that the sponsor

told us it was 94 percent, or 94 point -- I don't know whether there was a point. But anyway, that should be accurate.

DR. BLANCO: All right. Dr. Schultz?

DR. SCHULTZ: I can see that you guys are having a good time with this, but maybe I could shortcut this whole thing by saying that in the event of an approval decision, we will go through an extensive de-fluffing procedure for this label as we do with every other label.

(Laughter.)

You can count on that. And basically the recommendation that I'm hearing is that you want the label to be objective, balanced, talk about alternatives in a reasonable manner, and do it in a way that accurately reflects the data that was presented in the clinical trial. Is that a fair assessment?

DR. LEVY: Yes.

DR. SCHULTZ: Okay. Thank you. Now, if you want to continue, by all means, go.

(Laughter.)

DR. BLANCO: You just don't want us to have any fun.

DR. SCHULTZ: I do.

DR. BLANCO: All right. Any other comments that anyone else wants to make on this before we move on?

All right. Let's go -- move on to the -- all right. There are two others. Before we move out of -- okay. You have some comments on the user manual?

DR. JANIK: Yes. On the user manual, on 144, it says, "When using abdominal ultrasound guidance, the bladder should be full," implying that that's an option thing to do. Maybe it's just the way the sentence construction is, but it makes it seem like ultrasound is not a necessity. And also my concerns that I've raised before, that in the user manual the emphasis on ultrasound is extremely weak. I think there needs to be clarification of minimal training ability and that ultrasound is a requirement.

Is it possible to use transvaginal ultrasound with this? Have any of you tried it? No? No room? Okay, I thought so. Okay.

DR. BLANCO: All right. Any other comments on the labeling? There were two issues that were not in here that the FDA would like some comments on. And that was the -- the first issue was the issue of anesthesia, and I think we've already kind of

addressed that a little bit. And we're, I think -- and Barbara or anyone else, make sure I say this right -- but I think we have concerns, since the study was not designed to look at anesthesia needs, to make any kind of indication or claim or statement about that. Is that fair enough or do you want to get a little stronger?

DR. SHIRK: The other inference is that the general anesthesia is more hazardous than just office -- the local anesthesia. I don't think you can make that statement.

DR. LEVY: Yes. I just think that any reference to anesthesia just needs to be taken out of everything.

DR. BLANCO: Okay. That's pretty straightforward. Any other comments?

And then the other issue was the issue of antibiotics, which really hasn't been addressed anywhere. And is antibiotic prophylaxis needed or not needed? Should it be labeled? Should it be recommended? Any comments?

DR. LEVY: I don't think we have sufficient data to support or refute that one way or the other. The clinical judgment of the physician involved was used half the time anyway. I don't think

we've seen stratification on the data to say who got an infection, who didn't, what were the clinical situations involved with that? What was the definition of an infection? How is it -- you know, was it defined the same way? Certainly the cryopatients are going to have more discharge or may have more discharge. Was that the -- so I don't think I have enough data to say one way or the other.

I'd be very uncomfortable making any sort of recommendation, given what we have. We had equal numbers of, quote, "infections, unquote', in the two arms of the study -- five percent in both sides. We had 50/50 antibiotic use. I have no idea what to make out of that.

DR. BLANCO: Okay. Anybody else wants to make a comment? All right. So not enough information to be able to answer appropriately.

All right. Let's move on to number seven, training program. Please identify aspects of physician training which you believe are important -- patient selection, patient counseling, risk to pregnancy, duration, number of freezes --

DR. MITCHELL: Excuse me.

DR. BLANCO: Yes. You're excused. Go ahead.

DR. MITCHELL: Diane Mitchell. There were two other questions that I asked to be discussed. One was the contraindications, because we have the indications and --

DR. BLANCO: In all fairness to Dr. Harvey, she brought them up, but I didn't realize that you really wanted them discussed. So go ahead.

DR. MITCHELL: Just to remind you when you're looking at the contraindications about the size of the uterus. And then the other one that I mentioned was the dilation issue, which I think is mentioned in the patient pamphlet.

DR. BLANCO: All right. Well, let's go back. why don't you go back to the indications. Let's tackle that one first. I think we can all read it or we've already read it. Any comments on that? I think, Dr. O'Sullivan, you had some comments about childbearing. You want to change that on here or make any suggestions?

DR. O'SULLIVAN: Well, I think it should be clearly stated that patients with planned future pregnancy -- they should be cautioned not planned, because most pregnancies are not planned no matter what anybody says. But they should be made aware of that fact that if they do get pregnant, there can be

risks, as far as we know, to the pregnancy.

DR. BLANCO: All right. That's more a labeling issue than an indication issue. I think you

DR. O'SULLIVAN: That's a labeling issue. Indication issue, let me just re-read it.

DR. BLANCO: You're okay with the way this is worded?

DR. O'SULLIVAN: Let me just re-read it.

DR. BLANCO: Anyone else?

DR. DIAMOND: I have a different issue, which is going back to -- thinking about, again, of the draft document, one of the questions was who should be performing this procedure. In view of the concern potentially for needing to dilate the cervix, concern for potentially perforating, being able to recognize it when it happens, treat those complications that occurs, I would think this should a procedure and technique that at least at this point is limited to use by a physician and a physician familiar with conducting --

DR. LEVY: Uterine surgery.

DR. DIAMOND: -- D&Cs hysteroscopies.

DR. BLANCO: Okay. So as part of -- this actually hits on the training in terms of the way --

who should be able to do it and also to some extent ultrasound. Someone has to be able to read the ultrasound and know what they're seeing.

DR. DIAMOND: Right. Yes. Well, the physician knows that or in the presence of someone else who does, yes.

DR. BLANCO: Okay. Dr. Levy?

DR. LEVY: Okay. In terms of indication for usage, we don't have anything up there right at the moment in terms of size of the uterus. So looking at indications for usage, right there you could have a 16-week size uterus with a benign cause of bleeding, which is fibroids. We don't really say, but we really need to say that it's in a relatively normal size uterus or uteri ten weeks size or smaller. Certainly the study only documents efficacy or effectiveness in people with a ten centimeter or smaller. So I think we have to clarify that.

I still have a concern, though -- we talk about benign causes of bleeding. Does that mean that a patient with large submucous myoma would qualify for this? It's unclear to me from looking at the data, because I don't have the raw data, how many patients in this study actually had structural abnormalities that were appropriately managed or that were well

managed. Is that part of the failure that we're seeing in some of the other studies?

I mean I'm very comfortable saying benign causes of bleeding, but I'm very uncomfortable with the concept that we're mixing structural abnormalities with other abnormalities in the bleeding, and I'm not sure what to do with that, except to say that we definitely need to restrict the size of the uterus in this and that --

DR. SCHULTZ: Sorry. I just have clarification. This is Dan Schultz. I think one of the concerns was both the upper end and the lower end. Does the Panel want to make any recommendations? And we can do this either in terms of the indications or in terms of contraindications, warnings, precautions. We can do it on both sides. And if you tell us what your concerns are, I think we can work with the Company to fashion the appropriate label. But I think there was -- 1 heard discussion of both an upper limit and a lower limit, so you may want to give us a little help there.

'DR. BLANCO: Go ahead, Dr. Shirk.

DR. SHIRK: Well, my question would be, obviously, when we set up the initial protocol for the PMAs, that things like fibroids, polyps were

restricted for these procedures. I guess my question would be is it appropriate now to include those, including polyps, which may need to be removed, not knowing whether they're benign or malignant? And also is it fair to other companies that are going through the same process to suddenly grant this special dispensation for, quote, unquote, "all benign pathology?"

DR. BLANCO: Well, go back to the other one. That's why I had them put up the contraindications, because I guess we're talking about C, and so do you want to be more specific? I guess it just says weakness. It doesn't really address the fibroid.

DR. LEVY: And it's talking about having had a previous myomectomy. It's not talking about having fibroids now.

DR. JANIK: My understanding with your study is they were all pre-screened with either hysteroscopy or ultrasound. And if they had interuterine lesions, they weren't included. Am I correct? So if that's the case, it should be listed that this is lacking interuterine pathology,

DR. LEVY: Right.

DR. BLANCO: Yes. I think they can work

on the wording issues. You know, if they're having abnormal bleeding, that may be called pathology. So the issue is other things.

DR. JANIK: Structural pathology.

DR. BLANCO: Right. Thank you. Okay.

DR. LEVY: And they need to be pre-screened.

DR. BLANCO: All right. Any other comments? All right. These are the contraindications, and the size is on here, so I'll wait to -- on the next slide, so I'll wait to address it when we get there, on F, okay?

So let's go ahead and start with A. Any other contraindications that we need to talk about? and I guess my issue was, and maybe I didn't read the protocol in enough detail, but my understanding of the protocol was that all C-sections were excluded, and here I see classical and in the results I saw classical.

so I just wondered what was the original inclusion/exclusion criteria in the study, and were any patients with a low cervical transverse incision done? Were they treated3 And you don't have to answer now because you may not know the data, but I would say that we need to be consistent. So if there

were no patients treated with prior C-sections and that was an exclusion criteria for the study, then it shouldn't just be prior classical, it should be all C-sections.

Any other comments on any of these three? Dr. Diamond?

DR. DIAMOND: Another question I would raise, although I don't the answer, is what about uterine anomalies. If you do have a unicornua uterus or bicornua uterus, how is that going to affect this process in efficacy as well as safety?

DR. BLANCO: Well, I think with the issue of the structural abnormalities --

DR. JANIK: Structural.

DR. BLANCO: -- pretty much is going to wipe those out. And what about on B, it says, "A patient with known or suspected endometrial carcinoma or premalignant change of the endometrium, such as unresolved abnormal hyperplasia." Again, it's going back to the study and design. I believe they had an endometrial biopsy, if I'm not mistaken. And if that's the case, does this wording -- shouldn't this wording be a little bit stronger in terms of the documentation, that we don't have these problems?

DR. LEVY: I mean, basically, didn't they